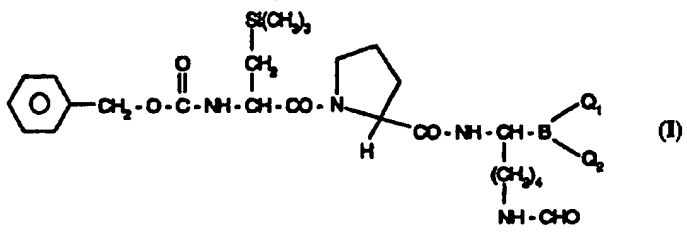
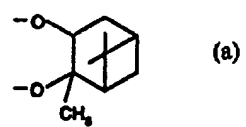


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<p>(21) International Application Number: PCT/EP96/03314</p> <p>(22) International Filing Date: 26 July 1996 (26.07.96)</p> <p>(30) Priority Data: 9515489.4 28 July 1995 (28.07.95) GB</p> <p>(71) Applicant (for all designated States except AT DE US): SANDOZ LTD. [CH/CH]; Lichtstrasse 35, CH-4002 Basle (CH).</p> <p>(71) Applicant (for DE only): SANDOZ-PATENT-GMBH [DE/DE]; Humboldtstrasse 3, D-79539 Lörrach (DE).</p> <p>(71) Applicant (for AT only): SANDOZ-ERFINDUNGEN VERWALTUNGSGESELLSCHAFT MBH [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).</p> <p>(72) Inventor; and (75) Inventor/Applicant (for US only): WIENAND, Anette [DE/DE]; Malteserstrasse 15, D-79423 Heitersheim (DE).</p> <p>(74) Common Representative: SANDOZ LTD.; Patents & Trade-marks Division, Lichtstrasse 35, CH-4002 Basle (CH).</p>		<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</p>
<p>(54) Title: BORONIC ACID DERIVATIVES</p> <div style="text-align: center;">  <p>(I)</p> </div> <div style="text-align: center;">  <p>(a)</p> </div> <p>(57) Abstract</p> <p>A compound of formula (I) wherein each of Q₁ and Q₂ is OH or Q₁ and Q₂ form together a residue of formula (a) have interesting pharmacological properties.</p>		

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5 **Boronic Acid Derivatives**

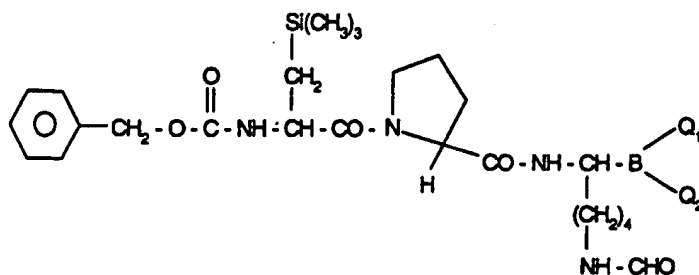
The present invention relates to boronic acid derivatives, a process for their production, their use as a pharmaceutical, e.g. as thrombin inhibitors, and pharmaceutical preparations containing them.

Thrombin is a trypsin-like serine protease fulfilling a central role in both haemostasis and
10 thrombosis. In the coagulation cascade, thrombin is the final key enzyme, proteolytically
cleaving fibrinogen to release fibrinopeptides A and B and generate fibrin, which can
then polymerize to form a haemostatic plug leading to occlusion of the vessels.
Thrombin generation is the final common result after activation of both the intrinsic
(= contact activation, e.g. by exposure of plasma to a non-endothelial surface) and
15 extrinsic (e.g. due to vessel wall damage and tissue factor release) coagulation pathways.

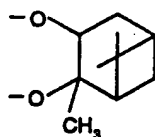
Extensive search for direct thrombin inhibitors has continued over the last years to
overcome the side-effects of conventional therapy, e.g. as with heparin, and to find orally
active compounds. The first direct thrombin inhibitors developed, e.g. hirudin and
hirulog-1, showed no advantages over heparin and no oral bioavailability.

20 One approach has been to provide peptidic derivatives of boronic acid as direct thrombin
inhibitors, e.g. as disclosed in WO 94/20526. However, there is still a strong need for
potent thrombin inhibitors having an improved selectivity over serine proteases, e.g.
trypsin, and being orally active.

Accordingly, the present invention provides a compound of formula I



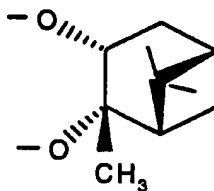
wherein each of Q_1 and Q_2 is OH or Q_1 and Q_2 form together a residue of formula (a)



(a)

- The trimethylsilyl-Ala residue, the Pro residue and the N^ϵ -substituted Lys residue may each have the L or D configuration. Preferably the Pro residue and the N^ϵ -substituted
- 5 Lys residue each have the L-configuration and the trimethylsilyl Ala residue the D-configuration.

The residue of formula (a) may exist in cis or trans configuration. Preferred residue of formula (a) is



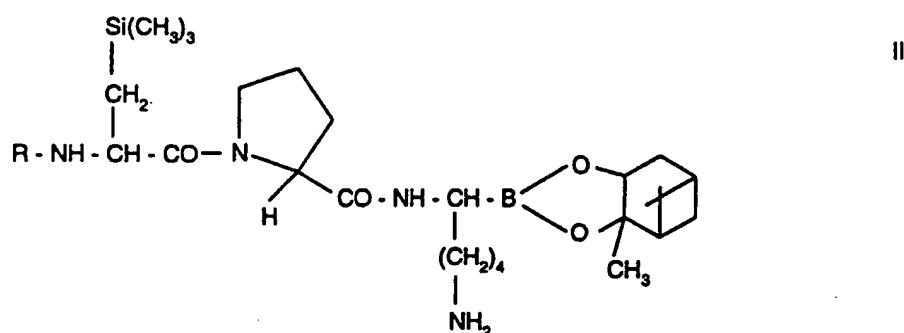
The present invention embraces all isomers and their mixtures.

- 10 The compounds of formula I wherein each of Q_1 and Q_2 is OH may exist e.g. in free or salt form. Salts include acid addition salts with e.g. organic acids, polymeric acids or

inorganic acids, for example hydrochloric acid. Preferably the compounds of formula I are in free form.

The present invention also includes a process for the production of the compounds of formula I, which process comprises

- 5 a) to produce a compound of formula I wherein Q_1 and Q_2 form together a residue of formula (a), formylating a compound of formula II



wherein R is benzyloxycarbonyl or another amino protecting group and, where required, replacing the amino protecting group R by a benzyloxycarbonyl group, or

- b) to produce a compound of formula I wherein each of Q_1 and Q_2 is OH, cleaving a
 10 compound of formula I wherein Q_1 and Q_2 form together a residue of formula (a),
 and recovering the compounds of formula I thus obtained wherein each of Q_1 and Q_2
 is OH in free form or in salt form.

The formylation step a) may conveniently be performed by using mixed anhydride of
 acetic acid and formic acid. The reaction may advantageously be carried out in an
 15 organic solvent, e.g. tetrahydrofuran.

R in compound of formula II is preferably benzyloxycarbonyl. When R is an amino
 protecting group other than benzyloxycarbonyl, it may be e.g. tert.-butoxycarbonyl or an
 amino protecting group as disclosed in "Protective Groups in Organic Synthesis",
 T.W. Greene, J. Wiley & Sons NY (1981), 219-287. When R in the compounds of
 20 formula II is other than benzyloxycarbonyl, the formylation may conveniently be carried

out before replacement of said protecting group R by benzyloxycarbonyl. The replacement of R by a benzyloxycarbonyl group may be performed in accordance with methods known and practiced in the art.

Compounds of formula II, used as starting materials, may be prepared as described in
5 WO 94/20526.

Process step b) may conveniently be performed by using e.g. NaIO₄, advantageously in an organic solvent, e.g. acetone.

The following examples are illustrative of the invention. All temperatures are in °C. Following abbreviations are used:

- 10 BoroLys = -NH-CH-(CH₂-CH₂-CH₂-CH₂-NH₂)B-
TMSal = trimethylsilylalanine
Boc = tert.-butoxycarbonyl
Z = benzyloxycarbonyl
THF = tetrahydrofuran
15 OPin = radical of formula (a) = pinanediol ester
Ac = CH₃CO-

Example 1: Z-D-TMSal-Pro-NH-CH[(CH₂)₄NHCHO]B-OPin

- a) 0.224 ml (5.95 mmol) formic acid and 0.530 g (5.2 mmol) acetic anhydride are stirred 2 h at 60°. The mixture is cooled to 0° and 1.86 g (3.00 mmol) of
20 Boc-D-TMSal-Pro-Boro-Lys-OPin dissolved in THF is added. After 10 min stirring at 0°, the reaction mixture is stirred at room temperature overnight. 80 ml of icewater is added, the solution extracted several times with ether and washed with brine. After drying over Na₂SO₄ and concentration in vacuo, the desired product is obtained as a white foam which can be crystallized from ether/hexane; mp: 93-99°;
25 $[\alpha]_D^{20} = -77.8^\circ$ (c = 0.5 in MeOH); FAB-MS: MH⁺ = 649.

- b) 324 mg (0.5 mM) of the Boc protected compound of step a) is stirred 3 h at room

- temperature with 3 ml conc. HCl/AcOH (9:1). After concentration in vacuo a white foam is obtained which is dissolved in THF. 1 eq benzyl chloroformate and 2 eq NEt_3 is added at 0° and the solution is stirred for another 3 h. Water is added and the product is extracted with ether, dried over Na_2SO_4 and concentrated in vacuo.
- 5 The residue is purified by flash chromatography (92:8, EtOAc/EtOH) to give an oil; $[\alpha]_D^{20} = -55^\circ$ ($c = 0.46$ in MeOH); FAB-MS: $\text{MH}^+ = 683$. mp: $68-69^\circ$.

Boc-D-TMSal-Pro-BoroLys-OPin used as starting material may be prepared as disclosed in WO 94/20526.

Example 2: Z-D-TMSal-Pro-NH-CH $[(\text{CH}_2)_4\text{NHCHO}]\text{B}(\text{OH})_2$

- 10 0.6 g (0.88 mM) of the pinanediol ester of Example 1 is dissolved in acetone, 20 ml 0.1 N NH_4OAc and 375 mg (1.76 mM) NaIO_4 are added and the solution is stirred for 2 days at room temperature. The precipitate is filtered off, the solution is extracted several times with ethyl acetate, dried over Na_2SO_4 and concentrated in vacuo. The oily residue is stirred in ether overnight and the product is obtained as white crystals;
- 15 mp. $88-108^\circ$; $[\alpha]_D^{20} = -54.1^\circ$ ($c = 0.51$ in MeOH); FAB-MS: $\text{MH}^+ + 72$ (reaction with matrix thioglycerine) = 621.

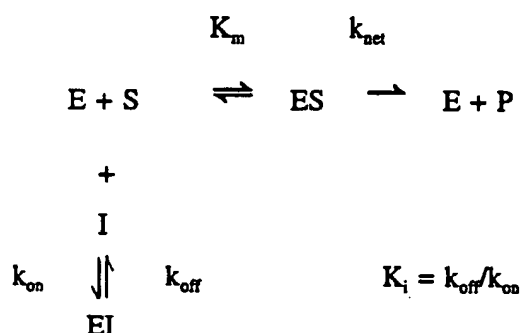
The compounds of formula I or a pharmaceutically salt thereof when each of Q_1 and Q_2 is OH exhibit pharmacological activity and are useful as pharmaceuticals.

- In particular, the compounds of formula I show trypsin-like serine protease inhibiting
- 20 properties, as indicated in the following test methods:

a) Enzyme inhibition kinetics

- Test substance is dissolved in cremophor/ethanol (1:1) or DMSO and diluted with distilled water to yield a 1 mM stock solution. Further dilutions are made into the assay buffer (100 mM sodium phosphate buffer, pH 7.4, containing 100 mM NaCl
- 25 and 0.1 % bovine serum albumin). Kinetic assays are performed using a 96-microwell plate; each well contains 50 μl substrate, 100 μl test compound and 100 μl enzyme in buffer. Final concentrations of substrate and enzyme are as

follows: 160 pM α -thrombin and 100 μ M Pefachrom TH ($K_m = 7.5 \mu$ M), 800 pM human plasmin and 200 μ M Pefachrome PL ($K_m = 44.1 \mu$ M), and 260 pM bovine pancreatic trypsin and 500 μ M Pefachrome TRY ($K_m = 145.7 \mu$ M). Assays are initiated by adding enzyme to solutions containing the substance to be tested and substrate. The release of p-nitroaniline from the hydrolysis of the substrate is followed for 30 min by measuring the increase in optical density at 405 nm with a Thermomax microwell kinetic reader (Molecular Devices, Menlo Park CA, USA). When the inhibited steady-state rate is achieved rapidly, the inhibition constant (K_i) is determined by fitting the data by weighted linear regression to the Dixon equation (Biochem. J. 1953, 55:170-171). For slow-, tight-binding inhibitors, the mechanism of inhibition may be described by the following scheme:



where E, S, P, and I are the enzyme, substrate, product (p-nitroaniline) and inhibiting substance to be tested, respectively, and k_{on} and k_{off} are the association and dissociation rate constants for the inhibition (Tapparelli *et al.*, J. Biol. Chem., 268 (1993), 4734-4741).

Progress-curve data for the formation of p-nitroaniline in the presence of different concentrations of inhibitor are fitted by nonlinear regression to the equation for the mechanism presented in the scheme (Morrison and Walsh, Adv. Enzymol. Relat. Areas Mol. Biol. 1988, 61:201-301). These analyses yield estimates for the apparent values of k_{on} , k_{off} and K_i which are corrected for the presence of substrate as described by Morrison and Walsh to give the true values. Under the described experimental conditions a K_i of 2.7 nM is observed for the compound of Example 1 and a K_i of 2.0 nM for the compound of Example 2.

Similar assays are used to assess the activity of the compounds of formula I on

plasmin, tissue plasminogen activator (t-PA), factor Xa (FXa) and trypsin.

		K _i in nM	
		Ex. 1	Ex. 2
5	Plasmin	2430	1218
	t-PA	1680	1542
	FXa	326	287
	trypsin	168	95.3

b) In vitro coagulation assays

In vitro coagulation assays are performed with pooled citrated human plasma. Substance to be tested or solvent are incubated with plasma for 10 min at 37°C prior to assay. Thrombin time(TT) determinations are performed at a final thrombin concentration of 5 U/ml. Activated partial thromboplastin time (APTT) is determined by incubating 0.1 ml plasma ± substance to be tested with 0.1 ml purified soya bean phospholipid in ellagic acid (Actin-FS) for 4 min at 37°C and followed by the addition of 0.1 ml CaCl₂ (50mM). In this test method, compounds of formula I significantly increase TT and APTT at a concentration of from 0.1 μM to 0.5 μM. With the compound of Example 1, prolongation of TT above 300 sec is achieved at 1.0 μM, elevation of APTT to 2x the control value is achieved at 1.8 μM.

c) In vitro platelet aggregation assay

Washed human platelets are prepared by a modification of the method of Ardlie (Br. J. Pharmacol. 1970, 19:7-17). Washed platelet suspension (0.46 ml) is kept at 37°C and stirred at 1100 rpm. After the addition of the substance to be tested or solvent, the platelets are maintained for 2 min before aggregation is induced by 1 nM human thrombin. The extent of platelet aggregation is quantitated by the maximum aggregation amplitude and inhibition of aggregation rate observed in the absence of inhibitor. In this test method, the compounds of Examples 1 and 2 inhibit platelet aggregation at a low nM concentration range: IC₅₀ = 11.2nM for the

compound of Example 1 and 9.8 nM for the compound of Example 2.

d) Venous Thrombosis

In the venous thrombosis model in the rat, a modification of the model described by Fredrich et al. (Blood Coag. Fibrinol., Vol. 5, (1994), page 243), the compounds of formula I prevent thrombus formation in a dose dependent manner. Using the compound of Example 1, thrombus formation is inhibited by 50 % at a dose (ED₅₀) of 0.96 mg/kg i.v. and at a dose of 15.9 mg/kg p.o. In this assay, the compound of Example 2 has an ED₅₀ of 0.43 mg/kg i.v.

e) Oral Effect Bioavailability

Administered to the same animals i.v. and p.o., the compounds of Examples 1 and 2 showed an oral effect bioavailability of 35% and 11%, respectively, in conscious aortic catheter rats.

In rhesus monkeys, the compounds of Ex. 1 and 2 are also administered i.v. and p.o. to the same animals, the oral effect bioavailability is > 15% for both compounds.

f) Clot Lysis

The method is a modification of that disclosed by Clozel et al. in J. Cardiovasc. Pharmacol., 12, 520-525, 1988. Male wistar rats are anaesthetized and the right jugular vein and the left carotid artery are exposed and cannulated. The cotton thread containing silicone tubing is inserted between the vein and the artery. Animals are pretreated with the compound to be tested via the jugular vein 20 min prior to ¹²⁵I-fibrinogen-labelled human clot insertion. Clot lysis is induced via the carotid artery by a bolus injection of t-PA followed by a 30 min infusion. Clot dissolution is monitored by placing a NaI crystal scintillation detector over the clot containing chamber. In this assay, the compound of Ex. 1 does not affect t-PA induced clot lysis and the compound of Ex. 2 even enhances clot lysis at a dose of 60µg/kg/min.

The compounds of formula I are therefore useful for preventing or treating thrombosis,

for example deep vein thrombosis, pulmonary embolism, in peri-operative antithrombotic cover, arterial thrombosis, unstable angina, disseminated intravascular coagulation (DIC), e.g. induced by sepsis trauma or certain cancers, coronary artery bypass surgery, for the control of coagulation and fibrinolysis, for inhibiting vascular remodelling (proliferation, migration of smooth muscle cells) following venous or arterial surgery or other forms of vascular injuries, e.g. percutaneous transluminal coronary angioplasty, allo- or xenotransplantation surgery, transplant vasculopathies, graft vessel diseases, acute or chronic restenosis and obstructive vascular atherosclerosis, .

For the above uses the required dosage will of course vary depending on the mode of administration, the particular condition to be treated and the effect desired. In general, however, satisfactory results are achieved at dosage rates of from about 0.01 to 15 mg/kg animal body weight. Suitable daily dosage rates for larger mammals, for example humans, are of the order of from about 1 to 750 mg/day, conveniently administered once, in divided dosages 2 to 4 x / day, or in sustained release form. When an extracorporeal blood loop is to be established for a patient 10 mg per liter may be administered intravenously. For use with whole blood from 1-10 mg per liter may be provided to prevent coagulation.

Compounds of formula I wherein each of Q_1 and Q_2 is OH may be administered in free form or in pharmaceutically acceptable salt form. Such salts may be prepared in conventional manner and exhibit the same order of activity as the free compounds. The present invention also provides a pharmaceutical composition comprising a compound of formula I, in free base form or in pharmaceutically acceptable salt form when each of Q_1 and Q_2 is OH, in association with a pharmaceutically acceptable diluent or carrier. Such compositions may be formulated in conventional manner.

Compounds of formula I may be administered by any conventional route, for example in particular enterally, preferably orally, e.g. in the form of tablets, capsules or drink solutions, or parenterally e.g. in form of injectable solutions or suspensions.

In accordance with the foregoing the present invention further provides:

- a) a compound of formula I or a pharmaceutically acceptable salt thereof when each of Q_1 and Q_2 is OH, for use as a pharmaceutical;
 - b) a method for preventing or treating disorders as indicated above in a subject in need of such treatment, which method comprises administering to said subject an effective amount of a compound of formula I or a pharmaceutically acceptable salt thereof when each of Q_1 and Q_2 is OH;
 - c) a compound of formula I or a pharmaceutically acceptable salt thereof when each of Q_1 and Q_2 is OH for use in the preparation of a pharmaceutical composition for use in the method as in b) above.
- 10 According to a further embodiment of the invention, the compounds of the invention may be employed as adjunct or adjuvant to other therapy, e.g. a therapy employing an anti-thrombotic agent, a fibrinolytic agent or an immunomodulatory agent, e.g. aspirin, heparin, t-PA, streptokinase, cyclosporins, ascomycins, brequinar, leflunomide or rapamycin or an analog thereof, azathioprine, methotrexate, mizoribine, mycophenolic acid or mycophenolate mofetil.

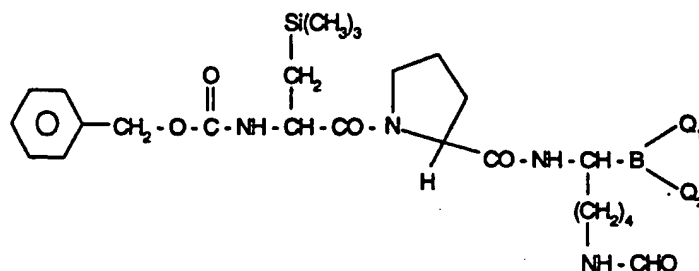
In accordance with the foregoing the present invention provides in a yet further aspect:

- d) a method for preventing or treating disorders as indicated above in a subject in need of such a treatment which method comprises administering to said subject an effective amount of i) a compound of the invention and ii) a second drug substance, said second drug substance being a therapeutic agent as indicated above; and
- e) a kit or combination for use in the method d).

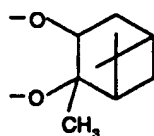
The compounds of formula I, particularly the compound of Example 2, have an interesting pharmacological profile, e.g. as disclosed above, as they exhibit an improved selectivity for thrombin and trypsin and a good oral bioavailability.

CLAIM

1. A compound of formula I



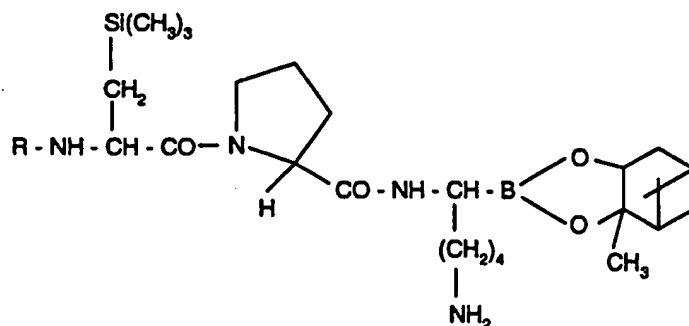
wherein each of Q_1 and Q_2 is OH or Q_1 and Q_2 form together a residue of formula (a)



(a)

in free form or, when each of Q_1 and Q_2 is OH, also in salt form.

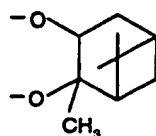
- 5 2. A process for the production of a compound of formula I to produce a compound of formula I wherein Q_1 and Q_2 form together a residue of formula (a), formylating a compound of formula II



II

wherein R is benzyloxycarbonyl or another amino protecting group and, where required, replacing the amino protecting group R by a benzyloxycarbonyl group, or carbonyl group.

3. A process for the production of a compound of formula I to produce a compound of formula I wherein each of Q_1 and Q_2 is OH, cleaving a compound of formula I wherein Q_1 and Q_2 form together a residue of formula (a),



(a)

- and recovering the compounds of formula I thus obtained wherein each of Q_1 and Q_2 is
- 5 OH in free form or in salt form.
4. A compound of formula I according to claim 1, or a pharmaceutically acceptable salt thereof when each of Q_1 and Q_2 is OH, for use as a pharmaceutical.
5. A method for preventing or treating thrombosis or for inhibiting vascular remodelling following venous or arterial injuries, in a subject in need of such treatment,
- 10 which method comprises administering to said subject an effective amount of a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof when each of Q_1 and Q_2 is OH.
6. A pharmaceutical composition comprising a compound of formula I according to claim 1 or a pharmaceutically acceptable salt thereof when each of Q_1 and Q_2 is OH, in
- 15 association with a pharmaceutically acceptable diluent or carrier therefor.
7. A kit or combination including a pharmaceutical composition according to claim 6 and a pharmaceutical composition comprising an anti-thrombotic agent, or fibrinolytic agent or an immunomodulatory agent.

INTERNATIONAL SEARCH REPORT

national Application No

PCT/EP 96/03314

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/06 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 94 20526 A (SANDOZ LTD.) 15 September 1994 cited in the application see the whole document and particularly page 10, formula IV ---	1-7
Y	EP 0 471 651 A (SANDOZ LTD.) 19 February 1992 see the whole document ---	1-7
P,Y	WO 95 20603 A (SANDOZ LTD.) 3 August 1995 see the whole document -----	1-7

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Beslier, L

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PL./EP 96/03314

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9420526	15-09-94	AU-A- 6208094	26-09-94
		EP-A- 0688336	27-12-95
		HU-A- 72735	28-05-96
		JP-T- 8507501	13-08-96
		NZ-A- 262415	28-10-96
		PL-A- 310940	08-01-96
		ZA-A- 9401501	04-09-95

EP-A-471651	19-02-92	AU-B- 643312	11-11-93
		AU-A- 8179291	20-02-92
		CA-A- 2048953	14-02-92
		IL-A- 99163	19-01-96
		JP-B- 2539965	02-10-96
		JP-A- 4330094	18-11-92
		US-A- 5288707	22-02-94

WO-A-9520603	03-08-95	AU-A- 1576495	15-08-95
		CA-A- 2179889	03-08-95
		EP-A- 0741747	13-11-96
